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U.S. High Production Volume (HPV) Chemical Challenge Program

CATEGORY DEVELOPMENT AND JUSTIFICATION, AND PROPOSED TEST PLAN FOR THE METAL CARBOXYLATES CATEGORY

Prepared by

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on behalf of

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

DECEMBER 20, 2002

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SUMMARY

The Metal Carboxylates Category includes 20 compounds that are metal salts of carboxylic acids. These compounds readily dissociate to the corresponding metal and carboxylic acid. HPV endpoints are fulfilled using a combination of data from the parent molecule, as well as for the dissociation products; that is, a metal salt and/or a carboxylic acid. Selected testing of the parent molecules has been proposed to further fulfill HPV endpoints. Robust summaries are provided for the parent molecules. Supporting data for the dissociation products are included within the remarks section of the Robust Summaries. The proposed testing is presented in the attached Test Plan matrix (Table I)

METAL CARBOXYLATES CATEGORY

The Metal Carboxylates Category (Category) includes 20 compounds that are metal salts of carboxylic acids (see list below). The Category is sponsored by the Metal Carboxylates Coalition (The Coalition) a consortium managed by Synthetic Organic Chemical Manufacturers Association's (SOCMA) Association Management Center. The Coalition is pleased to submit a Category development and justification, Test Plan and Robust Summaries for the following compounds sponsored under the U.S. High Production Volume (HPV) Challenge Program:

Chemical name	CAS#
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3
Phenol, Nonyl, Barium Salt	28987-17-9
Neodecanoic Acid, Cobalt Salt	27253-31-2
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Distearate	6865-35-6
Aluminum Tristrearate	637-12-7

Each compound includes a carboxylic acid moiety with a range of alkyl chain lengths and one of nine different metals cations (aluminum, barium, boron, cobalt, calcium, potassium, tin, zinc or zirconium).

Use Patterns for Metal Carboxylates

The metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are tailored for use in different products or chemical reactions.

In general the cobalt carboxylates are used as oxidative polymerization catalysts in many product areas. These areas include but are not limited to: Ink and paint driers; unsaturated polyester resins, and hydrodesulfurization in the manufacturing, making of DEET (diethyltoluamide). Some of these carboxylate compounds are used in oxygen scavenger plastics as well (for example, plastic bottles). The tire industry also uses cobalt carboxylate compounds as adhesion promoters in part of the tirestire manufacturing. These compounds help with the adhesion between the rubber in the steel cords. The metal (not salt) loadings range from 0.01-0.5% depending upon the application.

Potassium 2-ethylhexanoate is used as a catalyst for polyurethane systems (foams) and for unsaturated polyester resin systems (boats, shower stalls, etc.). Zinc carboxylate compounds are used as catalysts in paints and coatings; and in polyurethanes. They are used as heat stabilizers for PVC and as a heat and/or friction modifiers for lubricants and greases. Zinc carboxylate compounds can also be used as wetting agent for pigments in organic systems.

Zirconium carboxylate compounds are used as catalysts in inks, paints and coatings.

Common Characteristics of Metal Carboxylates

The Metal Carboxylates Category consists of 20 metal carboxylates. The compounds encompass nine metals (primarily in the divalent form) associated with carboxylic acids with varying chain lengths, differences in saturation and differences in branching[1]. The nine metals represented in this category are aluminum (Al), barium (Ba), boron (B), cobalt (Co), calcium (Ca), potassium (K), tin (Sn), zinc (Zn), and zirconium (Zr). Some of these metals are found in only one of the salts in the category, but most are found as the metal for several in more than one compound. For example, Co is the metal for eight of the twenty salts in the category. The carboxylic acids range in chain length from a shorter C2 alkyl chain (acetate) or a C3 propionate (as shown in Fig. 1a) to the longest C18 stearate (Fig. 1d) and the acids have either straight chains, e.g., stearate (Fig. 1d) or branched chains, e.g., 2-ethylhexanoic (Fig. 1b) or neodecanoic

[1] This category also includes one acid with an aromatic ring (nonylphenol barium salt) and two with cyclic rings (Zn and Co naphthenates).

acids (Fig. 1c). The metal carboxylates are functionally similar and have the same ionizable substituents, the metal cation, and the carboxylic acid group (RCOOH). The metal carboxylates are primarily divalent compounds and have two carboxylic acid moieties per molecule. The metal carboxylate salts are designed to add metals to chemical reactions; therefore, they are designed to readily dissociate into the free metal and free acid. Dissociation constants have been measured for 18 of the 20 metal carboxylate compounds. Dissociation data is presented below. Because of the importance of the effect of ready dissociation in the characterization of the toxicity of these compounds, it is discussed at length below.

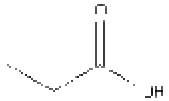
Dissociation Studies

One key characteristic of the compounds in the Metal Carboxylates Category is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). Dissociation is a reversible process and the portion of dissociated salt present is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for all of the 20 metal carboxylates. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

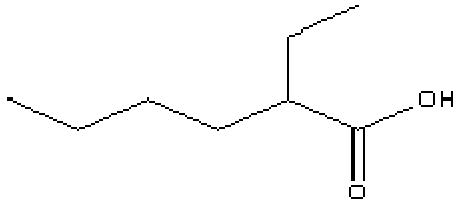
Dissociation studies have been conducted for 18 of the 20 compounds in the Metal Carboxylates Category. Results are presented in Table 1. Completion of the dissociation study with two aluminum stearate compounds was not possible due to low water solubility, although these compounds are also expected to readily dissociate (Crompton Corporation, personal communication). These studies indicate that significant dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the respective acids and metals to support the existing data for the salts within each subcategory and in the fulfillment of critical endpoints.

Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species which may be ionic, but are not necessarily so. The dissociation studies presented here were conducted according to OECD Guideline 112. The process can be generally represented as equation #1. The

Figure 1: Structures of Representative Carboxylic Acids Found in Metal Carboxylates



a



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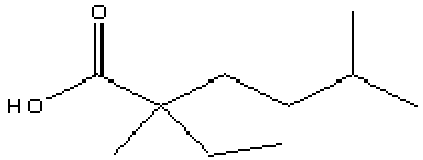


c

d

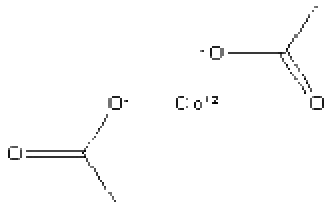
Table 1: Dissociation Constants for 20 Metal Carboxylates

Chemical	CAS#	pKa Values (mean of 3)*			
		pKa1	pKa2	pKa3	pKa4
Cobalt Acetate	71-48-7	7.750*	4.910		
Propionic Acid, Calcium Salt	4075-81-4	6.758*	4.745		
Propionic Acid, Cobalt (2+) Salt	1560-69-6	7.583*	4.848		
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0	6.893			
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6	8.448			
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7	6.409			
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8	6.992			
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9	5.813	7.033	7.648	8.235
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0	5.088			
Naphthenic Acids, Cobalt Salt	61789-51-3	6.737	8.004		
Naphthenic Acids, Zinc Salt	12001-85-3	7.310	9.176		
Phenol, Nonyl, Barium Salt	28987-17-9	8.342*	6.805	5.618	
Neodecanoic Acid, Cobalt Salt	27253-31-2	6.517			
Fatty Acids, C9-13-Neo-Cobalt Salts	68955-83-9	5.964			
Cobalt Borate Neodecanoate Complexes	68457-13-6	6.405			
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4	5.818			
Aluminum Distearate	300-92-5	---**			
Cobalt Stearate	13586-84-0	7.498			
Barium Distearate	6865-35-6	6.706			
Aluminum Tristrearate	637-12-7	---**			

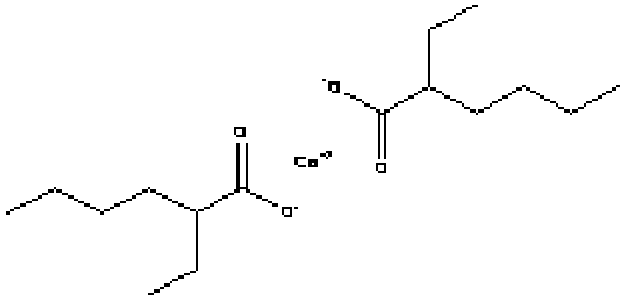
* For four compounds this is actually the pKb.

** The pKa values were not measured for two aluminium stearate compounds because the solubility was too low to be analyzed under the test guideline (OECD 112).

Figure 2: The Structures of Representative Metal Carboxylate Salts



a



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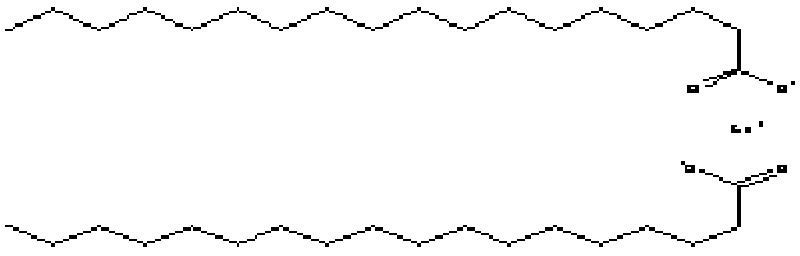


c

Equation #1

High pH Low pH

$$[RCOO^-]_x:[M^+]_x \; ? \; [RCOO^-]_x + [M^+]_x \; ? \; [RCOOH]_x + [MCl]_x$$

(salt) (Titrate with HCl ?) free acid and free metal

pKa and pH are equal when the parent compound (metal carboxylate salt) is 50% dissociated. The parent compounds, the metal carboxylate salts, are associated ionized molecules as shown in Figure 2. This figure shows three typical metal carboxylate salts with different chain lengths of the carboxylic acids: Co acetate (Fig. 2a), Co 2-ethylhexanoate (Fig. 2b), and Co stearate (Fig. 2c). Ionic charges are indicated for the acid and metal components of these salts (Figure 2).

The dissociation constant is important for two reasons. First, it determines the proportion of any specific acid or metal that is dissociated at a given pH. The free acid and corresponding free metal are often much different than the salt (ion pair) moiety in characteristics such as solubility, adsorption, and toxicity. The proportion of dissociation influences the behavior of the substance in the environment and bioavailablity of the acid and metal constituents of metal carboxylate salts.

The dissociation constants reported in Table 1 indicate that all 18 compounds tested have pKa (pKb) values (pKa1) in the neutral range (5.088 to 8.448). This indicates that in the neutral pH range, significant portions of the metal carboxylates will be dissociated. In addition, at the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates would be expected to be completely or nearly completely dissociated. This indicates that the absorption and any observed toxicity would be independent for the respective acid and metal when administered orally.

The dissociation constants show that at the pH of the stomach and at the pH of environmental media the important moieties are the ionized free acid and metal. Because of this, environmental fate, ecotoxicity, and mammalian toxicity of the free acid, or that for a simple salt (e.g., the sodium salt), can to serve as a surrogate data for the acid component of respective metal carboxylates. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data on of free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently (i.e., as the free metal and/or free acid).

Bioequivalency of Metal Carboxylates

Recent studies conducted to evaluate the "bioequivalency" (an estimate of bioavailability) of cobalt compounds, included three cobalt carboxylates and cobalt chloride. The solubility of these compounds in synthetic biological fluids (gastric juices, intestinal juices, several interstitial fluids, and cytosol) showed that these salts were completely dissociated and dissolved at gastric pH and cytosolic pH. The dissolution of these compounds ranged from 26.1% to 80.4 % of available cobalt at neutral pH (Table 2). The results for cobalt chloride and cobalt 2-ethyl-hexanoate were very similar at acidic and neutral pH. Cobalt neodecanoate and cobalt naphthenate showed similar levels of dissolution at acidic (gastric and cytosolic) pH, but smaller proportions of the metal component of these compounds were dissolved at neutral pH. The differences in dissolution for these metal carboxylates at neutral pH in synthetic body fluids could be related to differences in their dissociation constants (Table 1).

Table 2: Results of Extraction of Cobalt from Surrogate Biological Fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)	>91.6	100	>85.7	100
Intestinal pH (7.4)	>79.4	50.8*	45.4*	30.8*
Alveolar pH (7.4)	>68	>59.6	35.4*	26.1*
Interstitial pH (7.4)	78.4	>80.4	40*	43.1*
Serum	>85	>66.9	42.9*	46.6*
Intracellular pH (4.5)	>89.6	100	>79.1	>78.1

* maximum extraction level at 72 hours
All data is taken from Stopford et al. (unpublished) Bioequivalency Testing of Cobalt Compounds. Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute.

These data are valuable for three reasons:

1. They confirm the prediction that these compounds would be expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable at neutral pH (7.4).

2. The fraction of the three cobalt carboxylates that is dissolved at acidic and neutral pH is very similar for different acid constituents with a range of molecular weights and chain lengths. This finding greatly strengthens the extrapolation of the results to the entire category.

3. The work by Stopford et al. (unpublished) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

Supporting Data for Dissociation Products

1. Data for the parent compounds (i.e., the metal carboxylate salts) are provided in robust summary format. A set of robust summaries for each of the 20 metal carboxylate compounds are provided an appendix to this document.

2. In addition, when available, data for the dissociation products (metals and acids) are provided within the parent robust summary in the "Remarks" section.

Consistent with discussions between the Metal Carboxylates Coalition (the Coalition) and the EPA, data for the dissociation products (metals and acids) are recognized as being essential to understanding the environmental fate and toxicological characteristics of the respective metal carboxylate salts. Data for each individual acid (free acid or Na, K or Ca salt) and each individual metal (free metal, metal chloride, other simple metal salt) are useful in characterizing the hazard of a metal carboxylate compound. These data are available for compounds being sponsored in the HPV Challenge Program, chemicals sponsored in other existing chemicals testing, e.g., program (ICCA, SIDS) or pesticidal chemicals registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). It is important to recognize that most of the compounds in the metal carboxylate category are a combination of relatively common acids and metals. These data are clearly delineated as supporting data for the respective acids and metals and robust summaries were not prepared for individual acids or metals. If robust summaries for acids were available through the HPV Program, they are provided as attachments to the salt robust summaries.

1
Acids

When available, robust summaries for respective acids have been provided as appendices to each set of robust summaries for each respective salt. For example, the robust summaries for 2-ethylhexanoic acid were made available to the Coalition. These data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of the six 2-ethylhexanoate carboxylates. The 2-ethylhexanoic acid data is attached as Appendix 1 to each of six sets of robust summaries for the 2-ethylheaxanoate salts. Data for each of the acids is also summarized in Table III. Separate Robust summaries were not prepared by the Coalition for either individual metals or acids. Finally, because almost all of the acids are being sponsored under HPV Challenge or ICCA programs (e.g., neodecanoic acid, stearic acid, tall oil fatty acids). When this additional data for these acids becomes available, the Coalition will make a supplemental submission to EPA with data for these acids incorporated into the robust summaries for the compounds in the Metal Carboxylates Category.

Metals:

Data for most of the nine metals of interest are extensive. Rather than collect and review individual studies, the Coalition has relied upon well recognized and peer reviewed compendia (e.g., ATSDR Toxicological Profiles, WHO Environmental Health Criteria). Summarized data for the most appropriate forms of the metal (free metal or the chloride salt) are provided in the remarks section of the appropriate robust summary for each of the 20 metal carboxylates, as well as in tabular form in Table III. These well known compendia for metals are not provided with this submission, consistent with discussions with the EPA. These are readily available for EPA to review with this submission.

Summary

In summary, the key points relative to the Metal Carboxylates Category are:

- A common structure of RCOOH and a metal cation;
- Dissociation constants (pKa) in the circum neutral range (5.088 to 8.448);
    - Complete or nearly complete dissociation at gastric and cytosolic pH levels;
    - A moderate to high proportion of dissociation in the neutral pH range;
- General bioequivalency for salts with the same metal cation (for example, cobalt) and different acids or the chloride salt;

- Metal carboxylates have the same use pattern, to provide free metal ion to chemical reactions.
- Provision of data for the parent molecule or one or both of its dissociation products

SUBCATEGORIES

Rationale

The various carboxylic acids found in the 20 metal carboxylates in the Metal Carboxylate Category represent a range of chain lengths and other structural characteristics (e.g., branching, saturation, and the presence of ring substituents). These carboxylic acids can be grouped into six subcategories based on these structural characteristics and molecular weight (See Table 3 below), but they all have two things in common. They are all carboxylic acids and they are associated with a range of metals common to some or all of the subcategories.

Subcategories are listed in Table 3 and definitions are provided below with discussion of each subcategory and proposed testing. Testing needs for each subcategory are considered independently and are designed to allow each subcategory to stand alone. However, the Coalition believes that there is significant added value in evaluating these six subcategories as one overall category based on the common structural characteristics and ready dissociation as discussed previously.

Proposed Test Plan

The Coalition has taken a three pronged approach to category development for the metal carboxylates. First, the Coalition has collected and analyzed existing data for these twenty compounds. The existing data for the metal carboxylate salts have been summarized in robust summaries and ranked for reliability according to EPA Guidance.

As the second prong of the approach to category development, the Coalition has gathered existing data for the dissociation products, the respective metals and acids, and incorporated this data into the robust summaries and in the category justification for the metal carboxylate salts (as discussed above).

As the third prong, generation of additional data is proposed to support the Metal Carboxylates Category. This proposed testing program is outlined in Table I and the rationale provided below.

Table 3: List of Subcategories

Category 1 - Acetates/Propionates	***CAS#***
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6
Category 2 - 2-Ethylhexanoates	
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0
Category 3 - Naphthenates	
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3
Category 4 - Fatty Acids	
Neodecanoic Acid, Cobalt Salt	27253-31-2
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6
Category 5 - Barium Nonyl Phenol	
Phenol, Nonyl, Barium Salt	28987-17-9
Category 6 - Stearates and Tall Oils	
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Stearate	6865-35-6
Aluminum Tristearate	637-12-7

Proposed testing by subcategory

Subcategory 1- Acetates and Propionates

Table 4: Subcategory 1: Acetates and Propionates	***CAS#***
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6

Subcategory 1 compounds (Table 4) have identical acid components, either acetate (Figure 2a) or propionate (Figure 1a). These acids are identical with the exception that propionic acid has one more carbon than acetic acid. The chain lengths of 2 or 3 carbons are small relative to the other carboxylic acids in the category. These materials dissociate to form propionic acid or acetic acid (that have similar physico-chemical and environmental fate characteristics) and the relevant metal salt (Co or Ca). The acids are readily soluble, being relatively small in molecular weight. With the shortest carbon chain lengths in the Category, these compounds, are more readily bioavailable and potentially more toxic than the remaining 17 metal carboxylates that have longer chains and larger molecular weights.

Existing data for the compounds in this subcategory and the related metals and acids are summarized in Matrix 1. In order to support this subcategory, the Coalition proposes to generate the following data:

Physicochemical Properties:

Melting point, boiling point, water solubility, and partition coefficient are proposed to be determined for Co acetate and Co propionate. Boiling point and partition coefficient data will be generated for Ca propionate.

Environmental Fate Parameters:

Adequate biodegradation data are currently available for the two acid components in this subcategory, or will be after the completion of HPV testing for acetic acid. To supplement this information, biodegradation data will be generated for Co propionate to determine the effect, if any, of cobalt on biodegradation of the compound under ambient conditions. . Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for all three members of the subcategory.

Ecotoxicity:

Sufficient data is available for the salt for Ca propionate and for the dissociation products of Co acetate and Co propionate. Acute aquatic toxicity testing on to

fish, daphnia and algae is proposed to be conducted with for Co propionate to confirm that under ambient environmental conditions (i.e., neutral pH), the compound is not more toxic than its dissociation products.(or to generate data under ambient conditions for comparison to those for its dissociation products.)This testing will insure that upper bound toxicity data are generated for this compound and for the subcategory as a whole.. Sufficient data is available for the salt for Ca propionate and for the dissociation products for Co acetate.

Human Health Effects:

No acute mammalian toxicity and genotoxicity studies are proposed. All data elements are addressed with existing data on the salt or the dissociation products. There is substantial existing data for Ca propionate, including data from higher tiered mammalian studies (Matrix 1). However, the repeated dose and developmental data studies are from secondary literature references and thus could not be directly rated for reliability, but are believed to be adequate based on the long history of use of this compound as a food additive and preservative the reliability was Unassignable. There is no reproduction study for Ca propionate. For Co acetate, the Coalition will rely upon the data for the dissociation products. The Co data is available and the acetic acid data for the higher tiered mammalian studies is being addressed by the Acetic Acids and Salts Panel (The American Chemistry Council). The Test Plan will be modified and a supplemental submission provided when the acetic acid data becomes available (see Test Plan matrix, Table I). The repeated dose data element is addressed for the Co propionate based on the dissociation products and the remaining higher tiered studies are considered representative of the subcategory.

Subcategory 2 - 2-Ethylhexanoate Salts

Table 5: Subcategory 2 – 2-Ethylhexanoates	***CAS #***
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0

The second subcategory includes six metal salts of 2-ethylhexanoic acid (Table 5. Structures of the acids and a representative salts are shown in Figures 1b and 2b, respectively. The carboxylic acid, 2-ethylhexanoate, includes eight carbons and is a branched structure with an ethyl side chain on the second carbon. These branched compounds are substantially larger than those in subcategory 1 with a molecular weight range of 182 to 405 gm/M. With the exception of potassium, the metals in this subcategory are all divalent, i.e., are associated

with two 2-ethylhexanoic acid moieties, and the salts have a molecular weight range of 182 to 405 gm/M.

Available data are described in Matrix 2. In addition to the data available for the salt there is a complete set of robust summaries for the acid, 2-ethylhexanoate, which is being sponsored under the OECD SIDS program by the Oxo Process Panel of the American Chemistry Council. Summaries of available data for the metals for each respective salt are provided in Table II and Matrix 2. For this assessment, potassium and calcium have not been considered to be toxicologically significant and the potassium and calcium carboxylate salts are considered to have properties essentially the same as to the free acid.

The existing data for each 2-ethylhexanoate salt, the acid and the metals (with the exception of Ca and K) are shown in Matrix 2. In general, physicochemical property and environmental fate data are not available. The Coalition proposes to generate the following data:

Physicochemical Properties:

Generation of melting point, boiling point, solubility, and partition coefficient data are proposed for all six 2-ethylhexanoic acid salts (see Table I).

Environmental Fate Parameters:

Based upon demonstrated dissociation of these metal carboxylate salts and the refractory nature of the metals, biodegradation will depend primarily on the free acid. Data for biodegradation is proposed to be generated for the Zn and Sn 2-ethylhexanoate salts. These two salts were expected to represent a worst-case combinations of metal and acid for evaluating the subcategory as a whole. Since the acid (2- ethylhexanoate) has reliable biodegradation data, the Coalition will rely upon data for the acid alone to characterize the hazard of the potassium and calcium salts of 2-ethylhexanoate, based on the low order of toxicity for these metals. The remaining two salts are considered representative of the subcategory. Photodegradation and transport (fugacity) will be estimated using SAR models for all six compounds.

Ecotoxicity:

Reliable ecotoxicity data are not available for ecotoxicity for any of the salts in this subcategory, but are available for the 2-ethylhexanoic acid (Matrix 2). Extensive ecotoxicity data are also available for all of the metals. The Coalition believes that, in conjunction with new data to be generated on tin 2-ethylhexanoate, data for the parent acid and individual metals sufficient for hazard characterization of metal carboxylates in this subcategory (Matrix 2). Three ecotoxicity studies are proposed for the tin 2-ethylhexanoate salt. This

testing will insure that upper bound toxicity data are generated for this compound and for the subcategory as a whole under ambient pH conditions where complete dissociation may not occur. The remaining ecotoxicity values will be estimated using an SAR model (ECOSAR using new octanol water partition coefficient data to be generated). Although the existing ecotoxicity data for this subcategory is not especially reliable, the studies for the different compounds were performed by the same laboratory using the same procedures, and thus provide an indication of the relative toxicity of the compounds. The data for the acid and proposed ecotoxicity data generated on the tin salt plus estimated values using SAR models are expected to confirm the indications of relative toxicity within the subcategory.

Human Health Effects:

Existing data is available for mammalian acute (oral) toxicity and genotoxicity (*in vitro* and *in vivo*) for six of the 2-ethylhexanoate salts based on existing data for the salt and/or the dissociation projects (Matrix 2). Data are available for the higher tiered mammalian toxicity studies for all dissociation products of the six salts and the acid with the exception of the Zr 2-ethylhexanoate salt. For this compound, repeated dose data is available, but additional data on the developmental or reproductive toxicity of the metal are lacking. Because of this, and new data will be generated for the developmental and reproduction data elements for Zr 2-ethylhexanoate.

Subcategory 3 - Naphthenates

Table 6: Subcategory 3 - Naphthenates	***CAS #***
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3

The third subcategory consists of two compounds with naphthenic acid as the common “acid” for the Zn and Co naphthenates (Table 6). Zn naphthenate is considered the core chemical in this subcategory having reliable, existing data for most SIDS data elements. There is a substantial amount of existing data for the naphthenates, which is further supported by a nearly complete set of reliable studies for the copper salt, Cu naphthenate. This compound is not supported under the HPV Challenge Program, but has a FIFRA dossier[2]. Robust

[2] These studies were previously reviewed by the Office of Pesticide Programs to support the use of copper naphthenate under the FIFRA Deregistration Program. Because they did not exist, robust summaries for the Cu naphthenate studies were prepared by the Metal Carboxylates Coalition to facilitate comparison with Zn and Co naphthenate data. This is in contrast to acid data where robust summaries already existed, for the specific studies, and the Coalition did not want to rewrite or reinterpret studies or robust summaries already reviewed, or subject to future review, by the EPA as part of the HPV Challenge Program.

summaries have also been prepared for the copper salt (Matrix 3) and are provided with this submission per conversations with EPA. No additional data will be generated for the Cu salt. Data are also available for the naphthenic acid (and the sodium salt of naphthenic acid). All the existing data are summarized in Matrix 3.

To support this subcategory, the Coalition has proposed to generate the following additional data:

Physicochemical Properties

Data will be generated for partition coefficient for both Zn and Co naphthenates; and water solubility will be generated for Co naphthenate. Adequate data is available for the remaining physicochemical properties (see Matrix 3 and the Test Plan Matrix, Table I)

Environmental Fate Parameters:

Biodegradability will be determined for Co naphthenate (see Table 1). Adequate data is available for the Zn naphthenate. Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for both Co and Zn naphthenates.

Ecotoxicity:

No ecotoxicity testing is proposed for this subcategory. Adequate data are available for all three data elements for both the Co and Zn naphthenates, with the exception of aquatic plant toxicity for the Co salt, which are considered representative of the subcategory as shown in Matrix 3. Data are also available for the copper salt for these data elements (Appendix I of the Co and Zn Naphthenate Robust Summaries).

Human Health Effects:

Acute mammalian toxicity studies, genotoxicity (*in vitro* and *in vivo*) and higher tiered mammalian studies (i.e., repeated dose, reproduction, and developmental toxicity) are available for the core chemical Zn naphthenate and for the supporting chemical Cu naphthenate. Most of these data elements are also filled for the Co naphthenate with adequate data for the salt of the dissociation products; therefore, no additional studies are proposed for the chemicals in this subcategory (see Matrix 3 and Test Plan Matrix, Table I).

Subcategory 4 -: Neodecanoic and Fatty Acids

Table 7: Subcategory 5 - Neodecanoic and Fatty Acids	***CAS #***
Neodecanoic Acid, Cobalt Salt	27253-31-2
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6

The neodecanoic acid compounds (C10) and the C9-13 neo fatty acids listed above (Table 7) comprise Subcategory 4. The structure of neodecanoic acid provided in Figure 1c is a branched chain with three methyl groups on the terminal carbon in the primary chain.

The data for theses Co (and Co, borate) salts are presented in Matrix 4. Data for the metals and acids are provided in Tables II and III respectively. To support this subcategory, the Coalition proposes to generate the following data:

Physicochemical Parameters:

Data for four physico-chemical property data elements, melting point, boiling point, solubility, and partition coefficient, will be generated with the exception of boiling point for neodecanoic acid Co salt, which is addressed with existing data.

Environmental Fate Parameters:

A biodegradation study will be conducted on Co borate neodecanoate complexes. There are already adequate existing biodegradation data for the acid dissociation products of the other two compounds in this subcategory. Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for all three compounds in this category.

Ecotoxicity:

Acute aquatic toxicity to fish, *Daphnia* and aquatic plants will be generated for neodecanoic acid, Co salt. Data generated for this salt will be considered representative of the entire subcategory.

Human Health Effects:

Acute toxicity, bacterial mutagenicity and a chromosome aberration data will be generated with neodecanoic acid, Co salt. These data will be used to represent the fatty acids, C9-13-neo- Co Salts, and Co borate neodecanoate complexes (see Table I). No higher tiered studies are required based on existing data for the dissociation products. Data on fatty acid, C9-C13, neo and neodecanoic acid are currently being generated under the HPV Challenge Program by ExxonMobil as

part of the Neo Acids C5-C28 Category. When they become available, data from these studies will be incorporated into the robust summaries used to support the Neodecanoic and Fatty Acids Subcategory.

Subcategory 5 - Barium Nonyl Phenol

Table 8: Subcategory 5 - Barium Nonyl Phenol	***CAS #***
Phenol, Nonyl, Barium Salt	28987-17-9

The fifth subcategory is a single compound, nonylphenol, Ba salt (Table 8). There is an extensive data set for the "acid" nonylphenol (Table III). This compound dissociates and the metal Ba is present only as a small proportion of the overall molecular weight (24%). Barium has a low order of toxicity (Table II); therefore, any observed toxicity of the salt would be expected to be due primarily to the nonylphenol moiety. This acid has an aromatic ring at the acid end of the chain, as well as a single straight alkyl (C9) chain substitution which may vary in length which and which may occur at one or more the positions on the aromatic ring.

Physicochemical Properties:

Melting point, boiling point, water solubility, and partition coefficient studies are proposed for nonylphenol, Ba salt.

Environmental Fate Parameters:

The biodegradation data element is filled using nonylphenol data (see Matrix 5 and Table I). Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN).

Ecotoxicity:

These data elements are filled based on data for the dissociation products.

Human Health Effects:

Dissociation of nonylphenol Ba salt (Table 1) has been demonstrated and all mammalian toxicity data elements are filled using existing data for the dissociation products.

Subcategory 6 - Stearates and Fatty Acids, Tall-Oils

Table 9: Subcategory 6 - Stearates and Fatty Acids, Tall Oils	***CAS #***
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Stearate	6865-35-6
Aluminum Tristearate	637-12-7

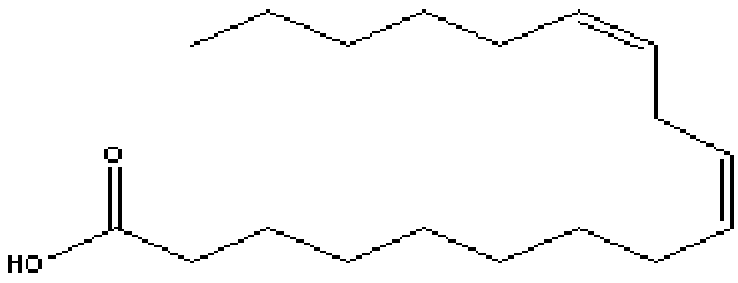
The sixth subcategory includes the metal carboxylates with stearates and fatty acids, tall-oils (Table 9) which contain primarily stearic (Fig. 3a), oleic (Fig. 3b), and linoleic (Fig. 3c) acids. These are the highest molecular weight compounds among the metal carboxylates with molecular weights ranging from 280.45 gm/M for fatty acid tall oil (linoleic) to 877.35 gm/M for Al tristearate. The metals in this subcategory are divalent or trivalent with a typical structure shown in Figure 2c (divalent Co stearate). To support this subcategory, the Coalition has relied on the fact that these compounds will dissociate and that the respective acid, such as stearate, is the chemical of interest. Dissociation was demonstrated and dissociations constants were reported for four of the six compounds in this subcategory. The exceptions were the two aluminum stearates, which had solubilities too low to allow analysis by the standard methods (OECD Guideline 112), but even these two compounds are expected to dissociate readily in water at neutral pH's and to be completely dissociated at the pH of the stomach (pH 1.2) similar to other metal carboxylates.

Stearic acid has a long history of use in foods and cosmetics. This compound is a member of the Aliphatic Acids Category and the Fatty Acids Tall Oil and Fatty Acid Related Substances Category that are being sponsored under the HPV Challenge Program.

Figure 3: Carboxylic Acids Found Subcategory 6

a

b



c

Likewise, tall oil fatty acids are part of the Tall Oil Fatty Acids and Related Substances Category that is also being sponsored in the HPV Challenge Program . Existing data for the salts in this subcategory and their associated acids and metals is summarized in Matrix 6.

The Metal Carboxylates Coalition is relying on the data for stearic acid and tall oil fatty acids to support this category and minimize unnecessary testing. When the Aliphatic Acids Category and Tall Oil Fatty Acids and Related Substances Category submission is made to the EPA under the HPV Challenge Program the robust summaries will become public domain. The Metal Carboxylates Coalition will then revise the current category development document to include the complete stearic acid and tall oil fatty acids data and will make a supplemental submission. The stearic acid salts will not be tested for these data elements, because stearic acid is a surrogate for the stearic acid salts based on known dissociation at neutral pH and at gastric pH.

Physicochemical Properties:

Melting point, boiling point, water solubility, and partition coefficient studies are proposed for all five metal carboxylate salts in this subcategory (Table 9 above) with the exception of existing data for melting point for Al distearate and Al tristearate.

Environmental Fate Parameters:

Biodegradation studies are proposed for Co stearate and Al tristearate, which are considered as to be representative of the subcategory. Since these compounds dissociate and the dissociated acid (stearic, oleic and linoleic acids) will be the moiety that degrades, the results would be expected to be the same for all five metal carboxylates in this subcategory. Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for the six metal carboxylates in this subcategory.

Ecotoxicity:

Acute aquatic toxicity data elements, fish, *Daphnia* and aquatic plants, will be filled with data for the dissociation products including data for stearic acid and tall oil fatty acids that is being sponsored as part of the Aliphatic Acids Category and the Fatty Acids Tall Oil and Fatty Acid Related Substances Category. Because of the very low water solubility for the salts in this subcategory, a reproduction study (rather than an acute toxicity studies) is proposed for aquatic toxicity testing. Chronic *Daphnia* (21-d) studies are proposed for fatty acids, tall oil, Co salts and Co stearate, and are considered representative of the subcategory.

Human Health Effects:

Data elements for acute oral toxicity and *in vitro* genotoxicity will be filled using existing data for the dissociation products. The Coalition will rely on the results of the Aliphatic Acids Consortium submission to address the three higher tiered data elements for stearic acid and stearic acid salts. When they become available, these data will be incorporated into the Metal Carboxylates Test Plan.

SUMMARY

The robust summaries for twenty metal carboxylates and supporting information for the dissociation products are submitted to the EPA to fulfill commitments under the High Production Volume Chemicals (HPV) Program. These twenty compounds are divided into six subcategories based on structural features. Recent dissociation studies for 18 of 20 compounds and bioequivalency studies for Co salts show that these metal carboxylate salts are partially dissociated at neutral pH relevant to mobility in the environment and certain physiological compartments, and completely dissociated at gastric pH. The potential effects of these compounds on the environment and mammals can be addressed using data for the salt or data for the respective acid and/or metal. The Test Plan reflects the combined use of salt and dissociation product data to address the HPV data elements. Proposed testing is focused on determination of physicochemical properties and environmental fate parameters. Based on the existing data, limited numbers of studies are proposed for ecotoxicity, acute mammalian toxicity, genotoxicity and the higher tiered mammalian studies (developmental and reproduction).

References

Stopford, W., J. Turner, D. Cappellini, and T. Brock. (unpublished) Bioequivalency Testing of Cobalt Compounds (Oct 15, 2002 Draft). Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute, Research Triangle Park, N.C.

Table I: Test Plan Matrix for the Metal Carboxylates Category

Table I: Test Plan Matrix	Physicochemical Prop.				Environmental Fate			Ecotoxicity				Human Health Effects					
	Melting point	Boiling point	Partition coefficient	Water solubility	Photodegradation	Dissociattion	Biodegradation	Fugacity	Acute fish	Acute invertebrate	Aquatic Plant toxicity	Acute oral toxicity	*In vitro* genotoxicity (bacterial)	*In vivo* genotoxicity (mammalian)	Repeated dose toxicity	Developmental toxicity	Reproductive toxicity
Subcategory 1																	
Cobalt Acetate	Test	Test	Test	Test	Calc	A	ADP *	Calc	ADP	ADP	ADP	A	A	A	ADP *	ADP *	ADP *
Propionic Acid, Calcium Salt	A	Test	Test	A	Calc	A	(A)	Calc	(A)	(A)	(A)	(A)	(A)	A	(A)	A	R
Propionic Acid, Cobalt (2+) Salt	Test	Test	Test	Test	Calc	A	Test	Calc	Test	Test	Test	ADP	ADP	ADP	ADP	R	R
Subcategory 2																	
Hexanoic Acid, 2-Ethyl, Potassium Salt	Test	Test	Test	Test	Calc	A	AO	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	ADP	ADP	ADP	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Ca Salt	Test	Test	Test	Test	Calc	A	AO	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	ADP	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Co (2+) Salt	Test	Test	Test	Test	Calc	A	R	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	A	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Zinc Salt	Test	Test	Test	Test	Calc	A	Test	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	ADP	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Zirconium Salt	Test	Test	Test	Test	Calc	A	R	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	A	ADP	Test	Test
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	Test	Test	Test	A	Calc	A	Test	Test	Test	Test	Test	A	ADP	ADP	ADP	ADP	ADP
Subcategory 3																	
Naphthenic Acids, Cobalt Salt	A	A	Test	Test	Calc	A	Test	Calc	A	A	R	A	A	R	ADP	R	R
Naphthenic Acids, Zinc Salt	A	A	Test	A	Calc	A	A	Calc	A	A	A	A	A	A	A	A	A
Subcategory 4																	
Neodecanoic Acid, Cobalt Salt	Test	A	Test	Test	Calc	A	ADP	Calc	ADP	ADP*	ADP*	Test	Test	Test	ADP*	ADP*	ADP*
Fatty Acids, C9-13-Neo-, Cobalt Salts	Test	Test	Test	Test	Calc	A	ADP	Calc	R	R	R	R	R	R	ADP*	ADP*	ADP*
Cobalt, Borate Neodecanoate Complexes	Test	Test	Test	Test	Calc	A	Test	Calc	R	R	R	R	R	R	ADP*	ADP*	ADP*
Subcategory 5																	
Phenol, Nonyl, Barium Salt	Test	Test	Test	Test	Calc	A	ADP	Calc	ADP	ADP	ADP	ADP	ADP	ADP	ADP	ADP	ADP
Subcategory 6																	
Fatty Acids, Tall Oil, Cobalt Salts	Test	Test	Test	Test	Calc	A	R	Calc	ADP *	Test/ CD	ADP *	ADP	ADP	ADP*	ADP*	ADP*	ADP*
Aluminum Distearate	A	Test	Test	Test	Calc	NA	R	Calc	ADP*	ADP*	ADP*	R	ADP	ADP*	ADP*	ADP*	ADP*
Cobalt Stearate	Test	Test	Test	Test	Calc	A	Test	Calc	ADP*	Test/ CD	ADP*	R	ADP	ADP*	ADP*	ADP*	ADP*

Table I: Test Plan Matrix for the Metal Carboxylates Category

Barium Stearate	Test	Test	Test	Test	Calc	A	R	Calc	ADP*	ADP*	ADP*	ADP	ADP	ADP*	ADP*	ADP*	ADP*
Aluminum Tristearate	A	Test	Test	Test	Calc	NA	Test	Calc	ADP*	ADP*	ADP*	ADP	ADP	ADP*	ADP*	ADP*	ADP*

Legend

Symbol	Description
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
(A)	Data rated as a Unassignable for reliability, but still considered adequate to address the given endpoint
ADP	Endpoint filled based on existing data for dissociation products (acid and metal)
ADP*	The Coalition relies upon acid data being generated under the HPV/ICCA Programs when metal data already exists.
NA	Not applicable due to physical/chemical properties
R	Endpoint requirement fulfilled using category approach.
CD	Chronic Daphnia
AO	Based on acid data only.

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
Physicochemical Properties							
Partition Coefficient (log K_{OW})							
Water Solubility, mg/L					839,000 at 0°C	4.32 E6 at 25°C	
Environmental Fate and Pathways							
Photodegradation							
Stability in water							
Monitoring Data							
Transport (Fugacity)							
Biodegradation							
Bioconcentration							
Ecotoxicity							
Acute Fish LC50 (in mg/L for metal ion)	96-h LC50 = 27 mg Al/L for the mosquitofish and 8.6 mg Al/L for the rainbow trout. Exposures were to aluminum chloride.	48-h LC50 = 150 mg Ba/L for the brown trout; 96-h LC50 = 1,080 mg Ba/L for the mosquitofish and >1,000 for the mummichog, *Fundulus heteroclitus.*	LC50 values range from 14 to 3400 mg B/L for juvenile fish. Data suggest that rainbow trout and zebra fish are the most sensitive species.	96-h LC50 = 333 mg Co/L for the carp and 1406 mg Co/L for the rainbow trout	96-h LC50 is >0.035 mg Sn/L for the mud dab	96-h LC50 values: 0.45 to 2.25 mg Zn/L for the carp; 0.29 and 0.42 mg Zn/L for the bluegill; and 0.093 - 0.815 mg Zn/L for the rainbow trout. The range of reported 96-h LC50 values (n=15) for freshwater fish was 0.14 to 0.78 mg Zn/L for tests conducted with zinc chloride or zinc sulfate	96-hr LC50 >20 mg Zr/L for rainbow trout exposed to $ZrCl_4$. For zirconium oxychloride, the 96-h LC50 for the bluegill is 15 – 270 mg Zr/L and for the fathead minnow it is 18 –240 mg Zr/L. For fathead minnows exposed to the zirconium salt of sulfuric acid the LC50 is 141 to 45 mg Zr/L.
Acute Invertebrate EC50 (in mg/L for metal ion)	48-hr EC50 = 3.9 to 27 mg Al/L for *Daphnia magna*. Exposures were to aluminum chloride.	96-h LC50 values range from 46 mg Ba/L for a crayfish to 238 mg Ba/L for the scud, *Gammarus pulex*	48-h EC50 values for *Daphnia magna* exposed to boric acid are 133 and 226 mg B/L. For sodium tetraborate pentahydrate, the 96-h EC50 for *Daphnia magna* is reported to be> 182 mg/L (> 27 mg B/L).	48-h EC50 values reported for *Daphnia magna* exposed to cobalt chloride range from 1.11 to 5.6 mg Co/L	48-h EC50 values for *Daphnia magna* exposed to tin chloride are 19.5 and 55 mg Sn/L	48-h EC50 values = 0.33 to 0.80 mg Zn/L for *Daphnia magna* and 0.07 to 0.86 mg Zn/L for several crustaceans including 3 daphnids.	21-d EC50 = 2 mg Zr/L for *Daphnia magna* exposed to $ZrCl_4$
Aquatic Plants EC50 (in mg/L for metal ion)	Effects on algae *Scenedesmus quadricauda* occur at 1.5 to 2.0 mg Al/L in 4-d tests. Exposures were to aluminum chloride.	96-hr EC50 = 25 mg Ba/L for the duckweed, *Lemna minor*	The 96-h EC50 for the aquatic vascular plant, *Lemna minor*, is > 60 mg/L. The 72-h EC50 for the green alga, *Scenedesmus subspicatus*, is 34 mg/L.	96-h EC50 = 0.522 mg Co/L for *Chlorella vulgaris* exposed to cobalt chloride.	72-h EC50 values for tin chloride range from 0.21 to >0.5 mg Sn/L for *Skeletonema costatum.* The 8-d EC50 for *Ankistrodesmus falcatus* is 12 mg Sn/L.	96-h EC50 = 0.0447 mg Zn/L for *Selenastrum capricornutum.* 72-h EC50 = 0.142 mg Zn/L for *Skeletonema costatum.*	96-h EC50 = 2.6 mg Zr/L for *Selenastrum capricornutum* exposed to $ZrCl_4$
Mammalian Toxicity							
Toxicokinetics, metabolism, distribution	Absorption is poor, usually 0.1 to 1%	Oral absorption has ranged from 0.7% to 85.0% indifferent animal	Pharmacokinetic data indicate that boron, usually administered as	The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats.	Inorganic tin compounds are not readily absorbed after oral or inhalation	Absorption of zinc in lab animals can vary from 10-40%. Half-life	Less than 1% of the daily intake of zirconium of humans is excreted in

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
distribution		85.0% indifferent animal studies.	usually administered as boric acid, is absorbed rapidly and virtually completely from the gastrointestinal tract and is rapidly excreted in the urine.	34% in the gut of rats. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine.	after oral or inhalation exposure. Absorption of Sn(II) from the G.I. tract is 2.85% in rats. Absorbed inorganic tin is excreted mainly in the urine.	10-40%. Half-life approx. 4-50 days in rats	humans is excreted in urine. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly.
Acute Oral LD50 (in mg/kg)	Rat: 380 to 3,730 mg/kg for aluminum chloride (equivalent to 77 to 753 mg Al/kg) with most values near 3,500 mg/kg; Mouse: 770 to 3,805 mg/kg for aluminum chloride (equivalent to 155 to 769 mg Al/kg).	Rat: 118 mg/kg for barium chloride (equivalent to 77.8 mg Ba/kg)	Rat & mouse: 400 to 700 mg B/kg for borax and boric acid; Guinea pig: 210 mg B/kg Dog, rabbit and cat: 250 to 250 mg B/kg	Rat: 19.1 to 85.5 mg Co/kg (cobalt chloride) and 55.4 to 72.5 mg Co/kg (cobalt sulfate). Mouse: 40.2 mg Co/kg (cobalt chloride) and 55.4 mg Co/kg (cobalt sulfate)	Lowest oral dose of stannous chloride that produced death: Rat: 473 mg Sn/kg; Mouse: 378 mg Sn/kg	Of the compounds zinc nitrate, zinc sulfate, zinc chloride and zinc acetate, zinc acetate was the most toxic, with oral LD50 values of 237 mg Zn/kg bw (rat) and 86 mg Zn/kg bw (mouse). The LD50 for zinc chloride in an oral exposure was reported to be 528 mg Zn/kg bw in rats and 605 mg Zn/kg bw in mice	Rat: 700 mg/kg for the tetrachloride salt (equivalent to 274 mg Zr/kg) and 3500 mg/kg for the oxychloride salt (equivalent to 1,792 mg Zr/kg).
Acute Inhalation LC50 (in mg/L)			The LC50 for sodium perborate tetrahydrate in rats is >74 mg/m^3.	Rat: 165 mg Co/m^3 as mixed cobalt oxides; > 10 mg Co/L for cobalt powder	Guinea pigs: exposure to tin (IV) chloride (3 mg/L for 10 minutes daily for several months) produced only transient irritation of the nose and eyes.	A 10-min exposure to 940 mg Zn/m^3 is lethal to rats	Severe, persistent interstitial pneumonitis has been produced in experimental animals exposed to airborne zirconium concentrations of 5 mg/m^3
Acute Dermal LD50 (in mg/kg)							
Skin Irritation	Solutions of 2.5 to 5.0 % aluminum chloride hexahydrate are mildly to moderately irritating to human skin when applied once daily for 3 days.		Boric acid and borax are mild to moderate skin irritants when applied to abraded skin.	Irritating	1% $SnCl_2$ produced pustules when applied to abraded rabbit skin, but not when applied to intact skin	Severe skin irritant to several species as a 1% ZnCl solution.	Certain zirconium salts (e.g. zirconium tetrachloride may cause irritation or caustic injury.
Eye Irritation					See acute inhalation above		Zirconium and its compounds are eye irritants
Repeated Dose Study	NOAEL = 62 mg Al/kg/day for a study with mice exposed to aluminum lactate via the diet; The LOAEL = 130 mg Al/kg/day based on neurobehavioral impairments.	NOAEL = 45 mg Ba/kg-day for female rats based on renal effects in the 1994 NTP study; LOAEL = 75 mg Ba/kg-day	NOAEL = 17.5 mg B/kg bw/day in a 2-year study with rats receiving boric acid or borax in the diet. LOAEL = 58.5 mg B/kg bw/day in this study.	LOAELs: 0.5 to 30.2 mg Co/kg/day (cobalt chloride) for oral exposures in rats	NOAEL = 32 mg Sn/kg/d for rats receiving stannous chloride via diet for 13 weeks (LOAEL = 95 mg Sn/kg/d). NOAELs = 63 and 164 mg Sn/kg/d for rats and mice, respectively, in 105 week feeding studies.	NOAELs were 53 to 565, and 104 mg Zn/kg/day for zinc sulfate fed in diet over 13 weeks to rats and mice, respectively. LOAEL = 12 mg Zn/kg/day as zinc chloride in rats exposed via water for 4 weeks.	NOAEL = 5 ppm in drinking water plus 2.6 ppm in feed for rats exposed over a lifetime to zirconium sulfate. No effects on rats and mice from exposure to 0.23 g Zr/kg/day of zirconium oxychloride.
Genetic Toxicity *in vitro*	Aluminum can cause genotoxicity under some circumstances, but has	Most *in vitro* genotox studies have found that barium chloride does not	Boric acid was not mutagenic in *Salmonella typhimurium* or in mouse	Cobalt compounds with a valence state of II, the form of cobalt released by	Negative results for stannous chloride with various bacterial systems;	In 11 *in vitro* studies with zinc chloride or zinc sulfate, negative results	Zirconium oxychloride and oxychloride hexahydrate are not

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
	circumstances, but has given mostly negative results in several *in vitro* mutagenicity assays.	barium chloride does not induce gene mutations with or without metabolic activation.	*typhimurium* or in mouse lymphoma cells and did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells.	form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast. Cobalt compounds with a valence state of III were weakly mutagenic in bacterial systems.	various bacterial systems; however, mutagenic effects seen in some studies with mammalian cells.	sulfate, negative results were reported with the exception of two ambiguous results and one weakly positive result.	hexahydrate are not mutagenic in *Salmonella typhimurium*. $ZrCl_4$ is not mutagenic in tests with *S. typhimurium* or the SOS chromotest.
Genetic Toxicity *in vivo*	Aluminum chloride is clastogenic in mice bone marrow cells when dosed via i.p. injection.		Existing data suggest that genotoxicity is not an area of concern following exposure to boron compounds in humans.	Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells.	Stannous chloride was not genetically active in the host-mediated assay and did not cause chromosomal aberrations in rats when administered orally. Stannous chloride was non-mutagenic in rats in the Dominant Lethal Assay	Studies on the induction of chromosome aberrations in bone marrow cells harvested from animals exposed to elevated levels of zinc yield equivocal results.	Zirconium oxychloride has been shown to induce chromosomal abnormalities in bone marrow cells of mice after oral exposure.
Developmental Toxicity / Teratology	Oral exposure to aluminum compounds may induce skeletal variations and delayed ossification. Teratogenic changes have not been associated with gestational exposure to aluminum.	Developmental toxicity was not observed in a single-generation reproductive/ developmental toxicity study in which rats and mice were exposed to barium chloride in drinking water at levels up to 2,000 ppm.	Developmental toxicity of boron has been demonstrated in mice, rats and rabbits, with rats the most sensitive species. Doses of boric acid equivalent to 58 mg B/kg bw/day and above, when administered to pregnant rats for the whole of gestation, cause a high resorption rate and retardation of fetal development. The NOAEL for the rat, the most sensitive species, was 9.6 mg B/kg bw/day.	Rat fetus LOAEL = 5.4 mg Co/kg/day (cobalt chloride); based on stunted pup growth. No teratogenic effects observed. Another study in rats gave NOAEL of 24.8 mg Co/kg/day for cobalt chloride. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride	Inorganic tin compounds have not been shown to be fetotoxic.	The offspring of pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any increase in the incidence of malformations. Several developmental toxicity studies were conducted with zinc sulfate on mice, rats, hamsters and rabbits, in general accordance with OECD Guideline 414; however the form of the zinc sulfate was not specified. Depending upon the form that was used, the calculated NOAEL values ranged from 6.8 mg Zn/kg bw for the mouse to 35.2 mg Zn/kg bw for the hamster.	In mice, offspring of dams who received zirconium during pregnancy had long-lasting behavioral changes.
Reproductive Toxicity	Reproductive success was not affected in a three-generation study with mice exposed to 49 mg Al/kg/day in drinking water and base diet. No reproductive effects were	Reproductive toxicity was not observed in a single-generation reproductive/ developmental toxicity study in which rats and mice were exposed to barium chloride in	Effects on reproductive organs occur in both males and females, but at higher levels in females. Effects on fertility were seen in rats and mice. Testicular lesions have	Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water.	Tin(II) chloride was reported to cause testicular degeneration in rats after prolonged feeding (1.5 to 9.2 mg Sn/kg/d for 13 weeks). Histopathological	Rats fed zinc chloride daily over an 8 week period demonstrated altered sperm chromatin structure with a LOAEL of 25 mg Zn/kg/d. The LOAEL for serious	Small fractions of zirconium were absorbed in female rats by the oral route, and the metal seemed to concentrate in the ovaries and produce hypervascularization.

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	reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg al/kg/day as aluminum lactate throughout gestation and lactation. An increased incidence of resorptions occurred in mice that were gestationally exposed to aluminum chloride by gavage, but no reproductive effects were found in rats similarly exposed to aluminum chloride, hydroxide, or citrate.	barium chloride in drinking water at levels up to 2,000 ppm.	Testicular lesions have been observed in rats, mice, and dogs administered boric acid or borax in food or drinking water in a number of studies. The lowest NOAEL for boric acid was based upon testicular effects (reduction in sperm count, inhibition of spermiation, and testicular atrophy) in male rats was reported to be 17 mg B/kg bw/day.	the diet or drinking water. Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks	Histopathological degeneration was seen in a few animals who were treated for 9 weeks at 30.5 mg Sn/kg/d and then sacrificed because of their moribund physiological state.	LOAEL for serious reproductive effects in female rats was 200 and 250 mg Zn/kg/d from exposure to zinc sulfate and zinc carbonate, respectively, in the diet.	hypervascularization.
Other Mammalian Toxicity Studies	Aluminum and aluminum compounds are not known to cause cancer in humans and none of the studies conducted on animals showed aluminum to be carcinogenic.	Oral exposure studies in rats and mice did not show significant increases in tumor incidences following chronic exposure to barium compounds for up to two years. Based on the available weight of evidence, barium is considered not likely to be carcinogenic to humans by oral exposure.	A 2-year feeding study showed no evidence of carcinogenicity in mice. There was no evidence of boric acid-related carcinogenicity in rats. Boron is classified by the US EPA as a Group D chemical (not classifiable as a human carcinogen).	The U.S. National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals.	Long-term bioassays with rats and mice exposed to stannous chloride in their diet and drinking water failed to produce any increase in incidence of tumors or the incidence of tumors was not clearly related to the administration of stannous chloride.	There is no adequate experimental evidence indicating that zinc salts administered orally or parenterally are tumorigenic.	Not classifiable as a human carcinogen. Rats administered 5 ppm of zirconium sulfate in drinking water for their entire lifetime did not have an increased incidence of tumors.

Table III. Summary of data available for carboxylic acids contained in sponsored metal carboxylates

Data Element		Acetic Acid	Propionic Acid	2-Ethyl Hexanoic Acid	Neodecanoic Acid	Fatty Acids, C9-C13 Neo	Naphthenic Acids	Phenol, Nonyl	Fatty Acids, Tall Oil	Stearic Acid
1	**Substance Information**									
1.0	CAS No.	64-19-7	79-09-4	149-57-5	26896-20-8	68938-07-8	1338-24-5	25154-52-3	61790-12-3	57-11-4
1.1	Molecular Formula	$C_2H_4O_2$	$C_3H_6O_2$	$C_8H_{16}O_2$	$C_{10}H_{20}O_2$	$C_9H_{18}O_2$ to $C_{13}H_{26}O_2$	Varies	$C_{15}H_{24}O$	$C_{18}H_{34}O_2$ (oleic) $C_{18}H_{32}O_2$ (linoleic)	$C_{18}H_{36}O_2$
1.2	Molecular Weight	60.05	74.08	144.22	172.27	158.24 to 214.35		220.36	282.47 (oleic); 280.45 (linoeic)	284.49
1.3	Structural Form									
2	**Physicochemical Properties**									
2.1	Melting Point (°C)	16.6	22	-118	48.1			24.5; 42		69.7
2.2	Boiling Point (°C)	117.9	141	228	252.1		132 to 243	290 to 302	160 to 210	376 - 383
2.3	Density		0.992				0.982			0.9408
2.4	Vapor Pressure		5 hPa	1.3×10^{-3} hPa				0.0000455 hPa		1.0 hPa
2.5	Partition Coefficient (log K_{OW})	-0.17	0.25 to 0.33	3.0 est.	3.8	3.4 to 5.4 est.		3.3; >3.8; 5.76	4.4 to 8.3 @pH 2; 3.5 to 7.4 @pH 7.5	8.2
2.6	Water Solubility (mg/L)	1×10^6	1×10^6	1,111 est. 25 IUCLID	80	2.3 to 210.5 est.		6.35	0.011 est.(oleic); 0.037 est (linoleic)	0.6 measured; 0.0035 est.
3	**Environmental Fate and Pathways**									
3.1.1	Photodegradation		50% after 4.7 years							
3.1.2	Stability in water									
3.2.1	Monitoring Data									
3.3.1	Transport (Fugacity)									
3.5	Biodegradation		95% in 10 d	Yes	11% in 28 days	2.3% in 28-d	Na salt: 50% in 24 d	7% in 28 d (Sturm); 78% in 40 d (BOD)	50% in 7 d; 56% in 28 d	72% in 28 d
3.7	Bioconcentration									
4	**Ecotoxicity**									
4.1	Acute Fish LC50 (mg/L)		67 to 85	70	37.2 to 181		5.6 to 16.3	0.13 5 to 0.95	10 to 20	> 1000
4.2	Acute Invertebrate EC50 (mg/L)		23 to 50	85	47 (*Daphnia*) 25 (*Acartia*.)		4.8 (calcium naphthenate, for copepod)	0.14 (*Daphnia*) 0.043 (Mysid)	55.7 (*Daphnia*)	> 0.09 (solubility limit; *Daphnia*)
4.3	Aquatic Plants EC50 (mg/L)		43 to 46	41			30.5 to 80.5 (*Navicula*)	0.027 to 0.323	0.8 to 9.0	> 1016
5	**Mammalian Toxicity**									
5.0	Toxicokinetics, metabolism, distribution		Is a normal intermediary metabolite in animals and humans	Approx. 75% of the oral dose excreted in urine within 24 h				10-20% of absorbed dose bioavailable; absorbed dose widely distributed in body		

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5.1.1	Acute Oral LD50 (mg/kg)		2,600 – 4,290 (rat)	1,600 – 3,200 (rat)	2,000 – 3,450 (rat)		3,000; 6,420 (rat); 3,550 (Na salt)	1,000 – 2,000 (rat)	>10,000	> 2000 (rat)
5.1.2	Acute Inhalation LC50 (mg/L)		>4.9 (rat)	>2.4 (rat)	> 3.0 mg/L; > 73 ppm; > 511 mg/m^3					
5.1.3	Acute Dermal LD50 (mg/kg)		500 (rabbit)	<5 ml/kg (guinea pig)	>3,640 (rat); > 3160 (rabbit)			>2,000 (rabbit)		
5.2.1	Skin Irritation		Severe (G. pig)	Slight to moderately irritating	Non-irritating (rabbit)			Irritant		
5.2.2	Eye Irritation		Mild to severe	Severely irritating	Irritant			Irritant		No irritation to mild irritation
5.4	Repeated Dose Study (NOAEL)		NOAEL = 2,000 mg/kg/d in a 90-d dog study; NOAEL = 1,320 mg/kg/d in a 1-yr rat study on the sodium salt	NOAEL = 300 mg/kg/d in a 13-w rat study; NOEL = 65 mg/kg/d	NOAEL = 50 ppm in a 3 month feeding study (30% preparation); NOAEL = 30 mg/kg/d in a 13-w oral dog study		NOAEL = 6 mg/kg/d in a rat 90-d oral study	NOAEL = 100 mg/kg/d for rat in a 28-d study; NOAEL = 50 mg/kg/d for rat in a 90-d study	NOAEL = 15% in diet for 28-d rat feeding study; NOAEL = 5% in diet or approx. 2,500 mg/kg/d in a 90-d rat study	LOAEL = 3000 ppm in diet in a rat 30-w feeding study (based on mortality)
5.5	Genetic Toxicity in vitro	Negative, non-clastogenic	Negative	Negative	Negative			Negative	Negative	Negative
5.6	Genetic Toxicity in vivo		Negative	Negative				Negative		
5.8.2	Developmental Toxicity / Teratology (offspring)	Rabbit NOEL= 1600 mg/kg/day		Rat NOEL = 100 mg/kg/d; Rabbit NOEL = 250 mg/kg/d	See result for reproduction			Fetus NOAEL = 300 mg/kg		
5.8.3	Reproductive Toxicity			NOEL = 100 mg/kg in a rat one-generation study	NOEL = 1500 ppm in a rat three generation study		No adverse effects in male rabbits over 10 wks from dermal exposure to an overbased calcium naphthenate in mineral oil	LOEL = 15 mg/kg; NOEL not found in a 3 generation rat study.	NOEL = 10% in diet in a rat two generation study	
6.0	Other Mammalian Toxicity Studies		Precancerous changes in stomachs of rats fed 4% (2640 mg/kg/d) in diet over lifetime		Not found to produce skin sensitization.			Estrogenic in several different assays		